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Well-done, Grilled Red Meat Increases the Risk of Colorectal Adenomas

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ABSTRACT

Red meat or meat-cooking methods such as frying and doneness level have been associated with an increased risk of colorectal and other cancers. It is unclear whether it is red meat intake or the way it is cooked that is involved in the etiology of colorectal cancer. To address this issue, we developed an extensive food frequency questionnaire module that collects information on meat-cooking techniques as well as the level of doneness for individual meat items and used it in a study of colorectal adenomas, known precursors of colorectal cancer. A case-control study of colorectal adenomas was conducted at the National Naval Medical Center (Bethesda, MD) between April 1994 and September 1996. All cases (n = 146) were diagnosed with colorectal adenomas at sigmoidoscopy or colonoscopy and histologically confirmed. Controls (n = 228) were screened with sigmoidoscopy and found not to have colorectal adenomas. The subjects completed a food frequency questionnaire and answered detailed questions on meat-cooking practices. We used frequency and portion size to estimate grams of meat consumed per day for total meat as well as for meat subgroups defined by cooking methods and doneness levels. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression, adjusted for age, gender, total caloric intake, reason for screening (routine or other), and several established risk factors for colorectal adenomas or cancer, including the use of nonsteroidal anti-inflammatory drugs, physical activity, and pack-years of cigarette smoking. There was an increased risk of 11% per 10 g/day (or 2.5 oz/week) of reported red meat consumption (OR, 1.11; CI, 1.03–1.19). The increased risk was mainly associated with well-done/very well-done red meat, with an excess risk of 29% per 10 g/day (OR, 1.29; CI, 1.08–1.54) *versus* an excess of 10% per 10 g/day (OR, 1.10; CI, 0.96–1.26) for consumption of rare/medium red meat. High-temperature cooking methods were also associated with increased risk; 26% per 10 g/day (OR, 1.26; CI, 1.06–1.50) of grilled red meat and 15% per 10 g/day (OR, 1.15; CI, 0.97–1.36) of pan-fried red meat consumption. There was an increased risk of colorectal adenomas associated with higher intake of red meat, most of which was due to the subgroup of red meat that was cooked until well done/very well done and/or by high-temperature cooking techniques, such as grilling. These results are consistent with the hypothesis that carcinogenic compounds formed by high-temperature cooking techniques, such as heterocyclic amines and polycyclic aromatic hydrocarbons, may contribute to the risk of developing colorectal tumors.

INTRODUCTION

Recently, an international panel of experts published a report "Food, Nutrition and the Prevention of Cancer: A Global Perspective" (1) in which it was concluded that there was "probable" evidence of increased risk of colon and rectal cancers with high intake of meat, especially red meat (defined as beef, pork, and lamb). It is unclear, however, whether cancer risk is related to the amount of red meat consumption *per se* or to certain meat-cooking practices that produce mutagens and carcinogens such as heterocyclic amines, polycyclic aromatic hydrocarbons, and possibly other agents (2–8). Using surrogates for exposure to these carcinogens such as doneness level, surface browning, method of cooking, and intake of gravy, epidemiological studies have thus far produced suggestive but inconsistent links to colon cancer risk (9–16).

To investigate the role of meat-cooking practices, we designed a meat cooking module within a FFQ.[2] Using this module, we attempted to disentangle the role of cooking methods and doneness levels from red meat consumption in a case-control study of colorectal adenomas. We studied adenomas because the majority of colorectal cancers are thought to arise from these benign precursor lesions (17), and it allows the evaluation of risk factors early in the colorectal neoplastic process among essentially healthy subjects. Furthermore, because changes in life-style factors after adenoma diagnosis are expected to be minimal, reporting of such information by adenoma patients would be less likely to be subject to recall bias than information from cancer patients.

MATERIALS AND METHODS

We conducted a case-control study of colorectal adenomas to evaluate meat-cooking practices and susceptibility in a medical center serving mainly active and retired military officers and their families. The study was approved by the Institutional Review Boards of both the National Cancer Institute and the National Naval Medical Center. Cases were patients who were diagnosed with colorectal adenomas at sigmoidoscopy or colonoscopy between April 1994 and September 1996. All index adenomas were histologically confirmed. Controls were selected among subjects without colorectal adenomas at sigmoidoscopy during the same time period and were frequency-matched to cases on age and gender. To be eligible for the study, cases and controls had to be residents of the study area, between ages 18 and 74 years, never have been diagnosed with Crohn's disease, ulcerative colitis, or cancer except nonmelanoma skin cancer.

The study was conducted in two phases: (*a*) at the hospital clinic; and (*b*) in the subject's home. The cases were identified from a colonoscopy clinic register, and informed consent was obtained during a return visit after histological confirmation of the adenomas. Some cases had flexible sigmoidoscopy before colonoscopy, whereas other cases had only a colonoscopy. Twice a week, a study staff member was present at a flexible sigmoidoscopy clinic where the controls were consented. Before the home visit, a self-administered FFQ was delivered to the subject's home. During the home visit, the FFQ was checked for completeness by a trained interviewer. In addition, an in-person interview was conducted to obtain information on meat-cooking practices, demographic background, medication and medical history, physical activity, sun exposures, tobacco and alcohol consumption, and occupational history. The home phase was identical for both cases and controls. Controls were interviewed at a median time of 90 days (10^{th} percentile, 40 days; 90^{th} percentile, 164 days) after sigmoidioscopy, and the cases were interviewed at a median time of 66 days (10^{th} percentile, 29 days; 90^{th} percentile, 121 days) after colonoscopy. In addition, subjects provided a blood sample during the clinic visit as well as multiple urine samples during the home visit.

The participation rates were 84% for the cases (244 of the 289 eligible cases identified) and 74% for the controls (231 of 314 eligible controls). The main reason for nonparticipation was subject refusal (12% of cases and 21% of controls), followed by illness (3% of cases and 4% of controls) and other reasons (1% of cases and 1% of controls). Of the 244 participants, 93 were

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[2] The abbreviations used are: FFQ, food frequency questionnaire; OR, odds ratio; CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drugs.

Table 1 *Potential risk factor characteristics of cases and control subjects*

	Cases (n = 146)	Controls (n = 228)	OR (CI)[a] (adjusted for age and gender)[b]
Female	24%	37%	0.5 (0.3–0.9)
NSAID use	19%	40%	0.5 (0.3–0.7)
Routine screening	30%	55%	0.3 (0.2–0.5)
Family history (1[st]-degree relative)	15%	12%	1.4 (0.7–2.5)
Age (yrs)	58 (46, 70)[c]	57 (46, 71)[c]	1.1 (0.6–2.0)
Body mass index	26 (22, 32)	26 (21, 32)	1.2 (0.8–2.2)
Smoking (pack-years)	4 (0, 57)	0 (0, 33)	1.6 (1.2–2.2)
Physical activity (h/week)	6 (0, 18)	7 (1, 16)	1.1 (0.7–1.6)
Calorie intake (kcal)	1488 (1043, 2617)	1488 (943, 2349)	1.2 (0.8–2.2)
Alcoholic beverage intake (g/day)	144 (0, 755)	117 (0, 732)	1.3 (0.8–1.7)
Fat intake (g/day)	48 (28, 94)	50 (22, 80)	1.4 (0.9–2.4)
Fruit/fruit juice intake (g/day)	196 (58, 510)	235 (65, 499)	0.8 (0.5–1.4)
Vegetable intake (g/day)	176 (78, 282)	180 (97, 308)	0.7 (0.4–1.1)

[a] ORs for age, body mass index, smoking, calorie, alcoholic beverage, fat, fruit/fruit juice, vegetable intakes were for 90[th] *versus* 10[th] percentiles.
[b] Age and gender were adjusted for each other.
[c] Median value (10[th] and 90[th] percentile).

excluded from the current report because of a history of previous adenomas. Two cases and three controls were excluded because of implausible dietary information, leaving 146 cases and 228 controls.

The validated FFQ, a modified version of the 100-item Health Habits and History Questionnaire (18), was used to obtain information on usual diet (frequency of consumption and portion size) approximately 1 year before sigmoidoscopy/colonoscopy. In addition, we developed a meat cooking module that included 23 meat items and has been validated using 12-day food diaries and a 24-h recall.[3] For meats prepared with variable cooking techniques, we obtained information on the typical level of doneness and cooking method. The five red meat items with doneness information (hamburger/cheeseburger, beef steak, pork chops/ham steaks, sausage/hot dogs, and bacon) are henceforth referred to as the "five red meats." For hamburger and steak, the doneness was determined as rare, medium-rare, medium, medium-well, well done, or very well done. For pork chops/ham steaks, sausage/hot dogs, and bacon, the doneness was defined as just until done, well done/crisp, and very well done/charred. This information was collected in two ways, verbally and by using photographs (19, 20). Those red meat items without doneness information are referred to as "other than five red meats." For the seven red meat items (the five red meats plus beef roast and pork roast) with cooking method information, henceforth referred to as the "seven red meats," the methods of cooking were classified as pan-fried, grilled/barbecued, oven-broiled, baked/roasted, or microwaved. Other red meat items, such as luncheon meats, beef stew, meatloaf, and liverwurst, are typically cooked in a standard way not fitting the above classifications. These are referred to as the "other than seven red meats."

We estimated the amount of meat intake (grams/day) from the frequency of consumption and portion size. For the five red meats, we estimated grams of meat consumed according to doneness level and created three different categories: (*a*) very well done; (*b*) well done; and (*c*) medium/rare. To calculate very well done categories, we added grams of very well done steak and hamburger; charred hot dog or sausage, bacon, and breakfast sausage; and very well done pork chops and ham steaks. To calculate the amount of meat in the well done categories, we added grams of well-done steak and hamburger; well-done/crisp hot dog or sausage, bacon, and breakfast sausage; and well-done pork chops and ham steaks. To calculate the medium/rare variable, we added up grams of meats cooked to the rare and medium level of doneness. A variable was also created for each of the cooking techniques (bake/roast, pan fry, grill/barbecue, microwave, oven broil, and other methods), reflecting the daily gram intake of each based on the seven red meats with such information.

ORs and 95% CIs were based on the same number of individuals and calculated using unconditional logistic regression (21). We present ORs reflecting the relative risk associated with a 10 g/day increase in reported daily consumption of meat. This provides us with the ability to directly compare ORs for the same amount of meat cooked in different manners. It also makes it easier to compare results between studies with different populations, where the amounts consumed might differ. The ORs for meat consumption were modeled using a linear relationship between the amount of reported meat intake and the log odds of disease. The linear relationship was checked by adding a quadratic term to the regression model, which in no case was statistically significant. Moreover, nonparametric logistic regression models using generalized additive models (22) also indicated that a linear model was appropriate for this data. We also present ORs comparing the risk of disease at the 90[th] *versus* 10[th] percentiles of meat intake, based on the same logistic regression models with continuous data. Tests for trend were calculated using the continuous data. Furthermore, we analyzed the data categorized in quintiles, according to the meat intake distribution in the control population. If more than 20% had zero consumption, all of these were included in the first quintile, reducing the numbers in the second.

All ORs were adjusted for age, gender, total caloric intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of NSAIDs. Additional adjustment for consumption of total fat, saturated fat, fruits, vegetables, fiber, or alcohol or for education, race, body mass index, bowel frequency, and family history of colorectal cancer did not substantially alter the findings.

To check for potential selection bias, we examined the risks for various subsets of the subjects, excluding cases with adenomas only in the right colon, cases with only rectal adenomas, and subjects who came to the clinic because of positive occult blood or visible blood in the feces.

RESULTS

Eighty-eight percent of the study population was of Caucasian origin. The median age of the cases and controls was 58 and 59 years, respectively (Table 1). Some notable case/control differences were a higher smoking history and lower percentage of NSAID use among cases compared with controls. There were no major differences in caloric intake or physical activity. A higher proportion of cases (26%) compared to controls (10%) were referred to the clinic because of gastrointestinal symptoms, such as blood in stool, occult blood, or diarrhea.

The 10[th], 50[th], and 90[th] percentile of various meats are: (*a*) 36, 84, and 156 g/day for total meat; (*b*) 8, 36, and 91 g/day for red meat; (*c*) 14, 42, and 99 g/day for white meat intake; (*d*) 3, 17, and 45 g/day for the five red meat items typically cooked to different doneness levels; (*e*) 0, 4, and 21 g/day for red meat cooked well done/very well done; (*f*) 0, 10, and 35 g/day for red meat cooked rare/medium; (*g*) 0, 3, and 19 g/day for well-done red meat; (*h*) 0, 0, and 1 g/day for red meat cooked very well done; (*i*) 0, 6, and 24 g/day for grilled/barbecued red meat; (*j*) 0, 0, and 7 g/day for grilled/barbecued, well-done/very well-done red meat; and (*k*) 0, 4, and 18 g/day for pan-fried red meat.

We found a nonsignificant increased risk of colorectal adenomas of 4% per 10 g/day increase in total meat intake (OR, 1.04; CI, 0.98–1.09), as shown in Fig. 1. This increased risk of 4% per 10 g/day

[3] Unpublished data.

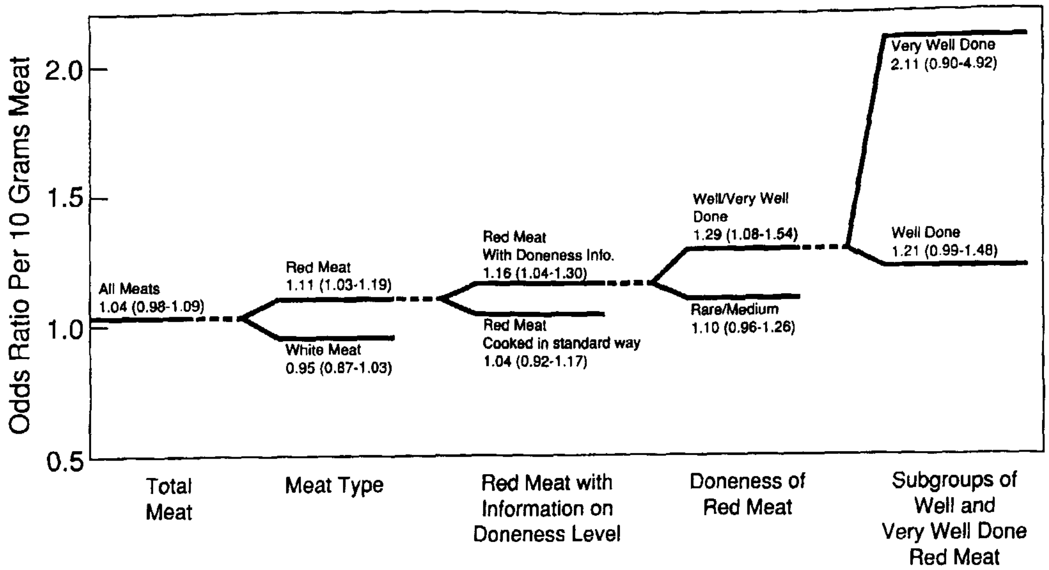

Fig. 1. ORs of colorectal adenomas (per 10 g/day or 2.5oz/week of meat intake) by intake level of meat cooked to different doneness levels. All ORs were adjusted for age, gender, total caloric intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of NSAIDs. Each of the five columns represents a different model: Model 1, *Total Meat*; model 2, *Meat Type*; model 3, *Red Meat with Information on Doneness Level*; model 4, *Doneness of Red Meat*; model 5, *Subgroups of Well- and Very Well-Done Red Meat*. Both variables within a column are from the same model. Red meat cooked in the standard way was retained in models 4 and 5 and similar in value to model 3 (data not shown). Rare/medium red meat was retained in model 5 and similar in value to model 4 (data not shown).

partitioned into a significant 11% per 10 g/day (OR, 1.11; CI, 1.03–1.19) risk increase for consumption of red meat and a nonsignificant decrease in risk of 5% per 10 g/day (OR, 0.95; CI, 0.87–1.03) for white meat intake. The test for trend for the red meat was significant (P = 0.005). The difference in risk between the red meat and white meat consumption was significant (P = 0.01). Similar results were observed in categorical analyses when we compared the lowest quintile to the 2nd, 3rd, 4th, and 5th quintiles; the ORs for red meat were 0.97 (CI, 0.43–2.20), 1.57 (CI, 0.72–3.41), 1.73 (CI, 0.78–3.82), and 2.28 (CI, 1.01–5.16), respectively.

Risk increased by 16% per 10 g/day (OR, 1.16; CI, 1.04–1.30) for the five red meats that are all cooked to variable levels of doneness, in contrast to a 4% increase per 10 g/day (OR, 1.04; CI, 0.92–1.17) for the other red meats (Fig. 1). We further partitioned the five red meats by doneness level and found that the risk increased by 29% per 10 g/day (OR, 1.29; CI, 1.08–1.54) for red meat cooked well done/very well done in contrast to 10% per 10 g/day (OR, 1.10; CI, 0.96–1.26) for red meat cooked rare/medium. The test for trend for well done/very well done was significant (P = 0.005). The difference in risk between the well-done/very well-done red meat and rare/medium red meat was nonsignificant (P = 0.1). Compared with the lowest quintile, the ORs for well-done/very well-done red meat were 0.82 (CI, 0.35–1.94), 1.07 (CI, 0.53–2.16), 1.18 (CI, 0.60–2.34), and 1.67 (CI, 0.85–3.27) for the 2nd, 3rd, 4th, and 5th quintiles, respectively. The results were essentially similar from the analyses when the doneness levels were calculated from the photographs.

When we subdivided the well done/very well done category, we observed an increased risk of 111% per 10 g/day (OR, 2.11; CI, 0.90–4.93) for red meat cooked very well done and 21% per 10 g/day (OR, 1.21; CI, 0.99–1.48) for well-done red meat.

Red meat was also partitioned according to cooking technique. Intake of grilled/barbecued red meat was associated with a significant 26% increase in risk per 10 g/day (OR, 1.26; CI, 1.06–1.50). The test for trend for grilled/barbecued meat was significant (P = 0.008). The difference in risk between grilled/barbecued meat and other methods of cooking meat was suggestive (P = 0.08). Compared with the lowest quintile, the ORs for grilled/barbecued red meat were 0.36 (CI, 0.07–1.83), 0.84 (CI, 0.42–1.66), 1.31 (CI, 0.70–2.48), and 1.87 (CI, 1.01–3.47) for the 2nd, 3rd, 4th, and 5th quintiles, respectively.

The risk was further elevated to 85% per 10 g/day (OR, 1.85; CI, 1.24–2.75) among subjects who ate their grilled meat cooked well done/very well done (Fig. 2).

Intake of red meat that was pan-fried was associated with a nonsignificant increase in risk of 15% per 10 g/day (OR, 1.15; CI, 0.97–1.36) and a 22% increase (OR, 1.22; CI, 0.92–1.61) for well-done/very well-done fried meat compared to rare/medium fried red meat intake. There was no excess risk associated with red meat that was microwaved, baked, or oven-broiled.

When we analyzed subgroups to check for potential bias due to recruitment strategy, the results were essentially unchanged. After excluding cases with only right-sided adenomas, the ORs for total red meat, well-done red meat, and grilled red meat were 1.09 (CI, 1.00–1.22), 1.29 (CI, 1.08–1.55), and 1.24 (CI, 1.03–1.48) respectively. The corresponding ORs after excluding subjects with rectal adenomas were 1.10 (CI, 1.00–1.12), 1.28 (CI, 1.06–1.54), and 1.22 (CI, 1.02–1.47), respectively; and the ORs were 1.11 (CI, 1.00–1.22), 1.34 (CI, 1.12–1.61), and 1.29 (CI, 1.08–1.54) after excluding subjects with positive occult blood or visible blood in the feces.

To evaluate the risk of colorectal adenomas and the amount of red meat consumed in this population, we also present the ORs based on the 90th *versus* the 10th percentile consumed among controls. These ORs were 1.69 (CI, 1.17–2.44) for well-done/very well-done red meat and 1.84 (CI, 1.67–2.91) for grilled/barbecued red meat. They are essentially identical to the estimated ORs for the 5th to the 1st quintiles obtained from a categorical model.

DISCUSSION

We conducted a case-control study of colorectal adenomas and found an increased risk of colorectal adenoma with increasing consumption of red meat. We then showed that this increase in risk was

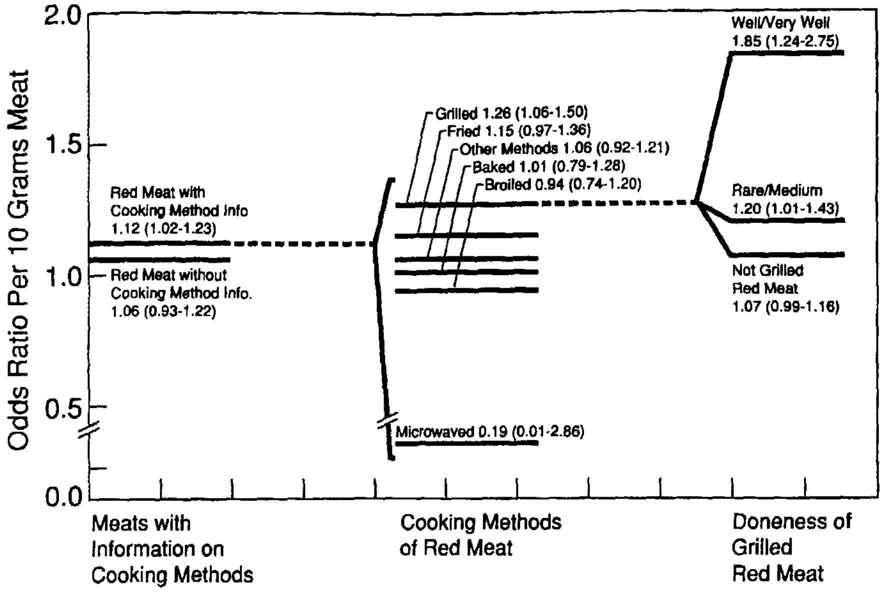

Fig. 2. ORs of colorectal adenomas (per 10 g/day of meat intake) by intake levels of meat cooked with different techniques and doneness levels. All ORs were adjusted for age, gender, total caloric intake, reason for screening (routine or other), physical activity level, pack-years of cigarette smoking, and use of NSAIDs. The variables contained in the first column (*Meat Information on Cooking Methods*) are from one model. The second column (*Cooking Methods of Red Meat*) depicts results from six different models for each cooking method. The variables in the third column (*Doneness of Grilled Red Meat*) are from one model.

primarily due to consumption of red meat cooked until well done/very well done and grilled or pan-fried red meat.

This study has several strengths. In this study, we have collected detailed information on cooking practices and doneness levels for specific types of commonly consumed meats. This is necessary to obtain accurate estimates of total intake by doneness and cooking method. It also allowed us to analyze risk by subtypes of meat cooked to different levels of doneness with various cooking techniques.

Another strength of this study is that cases had adenomas rather than cancer. As a consequence, their current dietary habits were less likely to have changed after diagnosis, and their responses to questions about usual dietary habits were less likely to be influenced by their treatment. In addition, the study had relatively high participation rates for a biologically intensive study with both a clinic and a home phase component. Finally, both cases and controls were recruited from a well-defined base of individuals, who were on active duty, retired from the uniformed services, or military dependents.

This study also has several limitations. We interviewed subjects after their diagnostic and treatment procedures were completed, so there is a potential for recall bias. However, as noted above, this is likely to be less of a problem when studying precancerous adenomas, which are completely removed by treatment, as compared to cancer. In addition, because the well-done meat intake hypothesis was not well established, patients were not advised by health care professionals at any stage of examination and treatment to reduce their intake of red meat or to modify its preparation.

Cases had a full colonoscopy, whereas the controls had only a flexible sigmoidoscopy; thus, some controls might have had undetected adenomas in the right-side colon. If risk factors for right-sided adenomas are similar to risk factors for left-sided adenomas, undetected adenomas among the controls would tend to attenuate our results. However, when the analysis was restricted to cases with left-sided colon adenomas, which are easily detectable by sigmoidoscopy, the results were essentially unchanged.

The associations between colorectal tumors and doneness and cooking methods are not consistent in previous studies (9, 11, 12, 14, 16, 23). One reason for the discrepancy may be that different cooking methods have generally been combined together within a question, leading to a dilution of the effect of specific cooking techniques. For example, pan-frying and deep-fat frying produce very different levels of heat on the surface of meat. Similarly, oven broiling, grilling, and pan frying cook meats differently. In the case of oven broiling, the fat and moisture drip out of the meat; in grilling, it falls onto a heated surface producing flames and higher temperatures; and in pan frying, the meat is cooked in the fat. In this study, we obtained details on both cooking methods and doneness level for each meat item rather than for all red meats lumped together as one item because it is reasonable to assume that people eat meats cooked to different levels and doneness depending on the type of meat. For example, a person may eat hamburger patty pan-fried and well-done, steak grilled/barbecued and medium, and bacon oven-broiled and very well done. Assuming that all red meats are cooked by the same technique to the same level of doneness loses much of the relevant information required to examine the hypothesis.

The two main factors that influence the production of pyrolysis products in cooked meats are time and temperature (24, 25). Epidemiologists have tried to identify surrogates for these two factors. Doneness of meat or external browning may be a reasonable surrogate for cooking time and temperature. Well-done meat has been associated with increased risk of colon, breast, lung, and stomach cancers (11–13, 15, 16, 26). We are now reporting a possible association between well-done red meat and colorectal adenomas with an increased risk of about 29% per 10 g/day (or 2.5 oz/week) of well-done/very well-done red meat consumed. Using cooking method as a surrogate for temperature, we found an increased risk of colorectal adenomas associated with grilled/barbecued red meat. There was an increased risk of approximately 26% for every 10 g/day increase in consumption of grilled/barbecued red meat.

In conclusion, we found evidence of increased colorectal adenoma risk with consumption of certain but not all red meats. We found that the excess risk was mostly confined to intake of well-done/very well-done red meat and meats cooked at high temperature such as grilled and possibly fried red meat. These results are consistent with cooking practices that produce carcinogens such as heterocyclic amines and polycyclic aromatic hydrocarbons.

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REFERENCES

1. American Institute for Cancer Research. World Cancer Research Fund and American Institute for Cancer Research (eds.). Food, Nutrition and the Prevention of Cancer: A Global Perspective. Washington, DC: American Institute for Cancer Research, 1997.
2. Adamson, R. H. Mutagens and carcinogens formed during cooking of food and methods to minimize their formation. *In:* V. T. DeVita, S. Hellman, and S. A. Rosenberg (eds.), Cancer Prevention, pp. 1–7. Philadelphia: J. B. Lippincott Co., 1990.
3. Sugimura, T., Sato, S., and Wakabayashi, K. Mutagens/carcinogens in pyrolysate of amino acids and proteins and in cooked foods: heterocyclic aromatic amines. *In:* Y. T. Woo, D. Y. Lai, J. C. Arcos, and M. F. Argue (eds.), Chemical Induction of Cancer, Structural Bases and Biological Mechanisms, pp. 681–710. New York: Academic Press, Inc., 1988.
4. Sugimura, T., Nagao, M., and Wakabayashi, K. Heterocyclic amines in cooked foods: candidates for causation of common cancers. J. Natl. Cancer Inst., *86:* 2–4, 1994.
5. Conney, A. H. Induction of microsomal enzymes by foreign chemicals and carcinogenesis by polycyclic aromatic hydrocarbons: G. H. A. Clowes Memorial Lecture. Cancer Res., *42:* 4875–4917, 1982.
6. Greenberg, A., Hsu, C. H., Rothman, N., and Strickland, P. T. PAH profiles of charbroiled hamburgers pyrene/B[a]P ratios and presence of reactive PAH. Polycyclic Aromatic Compounds, *3:* 101–110, 1993.
7. Wakabayashi, K., Totsuka, Y., Fukutome, K., Oguri, A., Ushiyama, H., and Sugimura, T. Human exposure to mutagenic/carcinogenic heterocyclic amines and comutagenic beta-carbolines. Mutat. Res., *376:* 253–259, 1997.
8. Mori, M., Totsuka, Y., Fukutome, K., Yoshida, T., Sugimura, T., and Wakabayashi, K. Formation of DNA adducts by the comutagen norharman with aromatic amines. Carcinogenesis (Lond.), *17:* 1499–1503, 1996.
9. Steineck, G., Gerhardsson De Verdier, M., and Overvik, E. The epidemiological evidence concerning intake of mutagenic activity from the fried surface and the risk of cancer cannot justify preventive measures. Eur. J. Cancer Prev., *2:* 293–300, 1993.
10. Knekt, P., Steineck, G., Jarvinen, R., Hakulinen, T., and Aromaa, A. Intake of fried meat and risk of cancer: a follow-up study in Finland. Int. J. Cancer, *59:* 756–760, 1994.
11. Gerhardsson De Verdier, M., Hagman, U., Peters, R. K., Steineck, G., and Overvik, E. Meat, cooking methods and colorectal cancer: a case-referent study in Stockholm. Int. J. Cancer, *49:* 520–525, 1991.
12. Schiffman, M. H., and Felton, J. S. Refried foods and the risk of colon cancer. Am. J. Epidemiol., *131:* 376–378, 1990.
13. Ronco, A., De Stefani, E., Mendilaharsu, M., and Deneo-Pellegrini, H. Meat, fat and risk of breast cancer: a case-control study from Uruguay. Int. J. Cancer, *65:* 328–331, 1996.
14. Muscat, J. E., and Wynder, E. L. The consumption of well-done red meat and the risk of colorectal cancer. Am. J. Public Health, *84:* 856–858, 1994.
15. Ward, M. H., Sinha, R., Heineman, E. F., Rothman, N., Markin, R., Weisenburger, D. D., Correa, P., and Zahm, S. H. Risk of adenocarcinoma of the stomach and esophagus with meat cooking method and doneness preference. Int. J. Cancer, *71:* 14–19, 1997.
16. Probst-Hensch, N. M., Sinha, R., Lin, H. J., Longnecker, M. P., Witte, J. S., Ingles, S. A., Frankl, H. D., Lee, E. R., and Haile, R. W. Meat preparation and colorectal adenomas in a large sigmoidoscopy-based case-control study. Cancer Causes Control, *8:* 175–183, 1997.
17. Eddy, D. M. Screening for colorectal cancer. Ann. Intern. Med., *113:* 373–384, 1990.
18. Smucker, R., Block, G., Coyle, L., Harvin, A., and Kessler, L. A dietary and risk factor questionnaire and analysis system for personal computers. Am. J. Epidemiol., *129:* 445–449, 1989.
19. Sinha, R., Rothman, N., Salmon, C. P., Knize, M. G., Brown, E. D., Swanson, C. A., Brown, E. D., Rhodes, D., Felton, J. S., Levander, O. A., and Rothman, N. Heterocyclic aromatic amine content of beef cooked by different methods and degrees of doneness and beef gravy made from roast. Food Chem. Toxicol., *36:* 279–288, 1998.
20. Sinha, R., Knize, M. G., Salmon, C. P., Brown, E. D., Rhodes, D., Felton, J. S., Levander, O. A., and Rothman, N. Heterocyclic amine content of pork products cooked by different methods and to varying degrees of doneness. Food Chem. Toxicol., *36:* 289–297, 1998.
21. Hosmer, D. W., and Lemeshow, S. Applied Logistic Regression. New York: John Wiley & Sons, 1989.
22. Hastie, T., and Tibshirani, R. Generalized Additive Models. London: Chapman & Hall, 1990.
23. Schiffman, M. H., Van Tassell, R., and Andrews, A. W. Epidemiologic studies of fecal mutagenicity, cooked meat ingestion, and risk of colorectal cancer. Prog. Clin. Biol. Res., *340E:* 205–214, 1990.
24. Gross, G. A., Turesky, R. J., Fay, L. B., Stillwell, W. G., Skipper, P. L., and Tannenbaum, S. R. Heterocyclic aromatic amine formation in grilled bacon, beef, and fish and in grill scrapings. Carcinogenesis (Lond.), *14:* 2313–2318, 1993.
25. Knize, M. G., Dolbeare, F. A., Carroll, K. L., and Felton, J. S. Effects of cooking time and temperature on the heterocyclic amine content of fried-beef patties. Food Chem. Toxicol., *32:* 595–603, 1994.
26. Sinha, R., Kulldorff, M., Curtin, J., Brown, C. C., Alavanja, M. C., and Swanson, C. A. Fried, well done red meat and the risk of lung cancer in women. Cancer Causes Control, *9:* 621–630, 1998.